Pharmacovigilance Practical Notes

GENERAL STEPS TO START PV ACTIVITY FOR ANY PRODUCT

1- Legal status of product??

2- Required PV documents requested from regulatory authority.

3- Time line for submission of PV documents.

4- Literature screening for this product in specific (regardless usual routine research of each week)

5- Read all medical data about product.

6- Collect post marketing data if product marketed

7- If product marketed do not miss to check on PBRER data lock point & PBRER last submission date.

8- Define most updated safety concern profile of innovator (identified / potential / missing).

9- Define most updated risk management plan of innovator, including or PV activities in this RMP.

10- Get most updated SmPC & PIL of innovator & check your product SmPC & PIL with it.

11- Start to put your plan to do RMM.

12- Prepare your product RMP.

13- Submit it if required.

14- Do not miss weekly basis literature screening.

15- Do not miss follow up pf world wide newsletters of PV such as WHO, EMA..

16- Do not miss training plan to your concerned departments on common PV activities.

17- Do not miss to collect all your product with regard to weekly – monthly – yearly plan.

18- Do not miss updated monthly schedule of PBRER submission according to monitor EMA list of PBRER dates (which updated monthly)

- Adverse drug reactions

Council for International Organizations of Medical Sciences (CIOMS)

Frequency of adverse drug reactions (CIOMS)

• Very common	• >= 1/10
• Common (frequent)	• > = 1/100 and < 1/10
• Uncommon (infrequent)	• >= 1/1000 and < 1/100
• Rare	• >= 1/10000 and < 1/1000
• Very rare	• < 1/10000

Types of adverse drug reactions

- Type A
- Augmented pharmacologic effects - dose dependent and predictable (medicine actions) are those which are due to (exaggerated) pharmacological effects. Type A effects tend to be fairly common, dose related (i.e. more frequent or severe with higher doses) and may often be avoided by using doses which are appropriate to the individual patient. Such effects can usually be reproduced and studied experimentally and are often already identified before marketing.
- Type B:
- Bizarre effects (or idiosyncratic) - dose independent and unpredictable (Patient reactions) characteristically occur in only a minority of patients and display little or no dose relationship. They are generally rare and unpredictable, and may be serious and are notoriously difficult to study. Type B effects are either immunological or non-immunological and occur only in patients, with - often unknown - predisposing conditions. Immunological reactions may range from rashes, anaphylaxis, vasculitis, inflammatory organ injury, to highly specific autoimmune syndromes. Also non-immunological Type B effects occur in a minority of predisposed, intolerant, patients, e.g. because of an inborn error of metabolism or acquired deficiency in a certain enzyme, resulting in an abnormal metabolic pathway or accumulation of a toxic metabolite. Examples are chloramphenicol aplastic anaemia and isoniazid hepatitis.

- **Type C**
- Chronic effects refer to situations where the use of a medicine, often for unknown reasons, increases the frequency of a "spontaneous" disease. Type C effects may be both serious and common (and include malignant tumours) and may have pronounced effects on public health. Type C effects may be coincidental and often concern long term effects; there is often no suggestive time relationship and the connection may be very difficult to prove.
- **Type D**

  Delayed effects (dose independent)

  Carcinogenicity (e.g., immunosuppressants)

  Teratogenicity (e.g., fetal hydantoin syndrome)
- **Type E**

  End-of-treatment effects
- **Type F**

  Failure of therapy

ADR Processing – Collection of reports

Suspected medicine

- Name (INN and brand name)
- Strength (concentration)
- Dose, Frequency
- Dosage form
- Route of administration
- Indication for use
- Duration of use, date started, date stopped
- Batch number (especially for vaccines)

An identifiable patient

At least 1 of the following:

- Patient initials
- Sex
- Weight
- Age at time of reaction or date of birth

Suspected adverse reaction

- Description of the reaction
- Expectedness of the reaction (in accordance with the approved product information)
- Seriousness of the reaction
- Date the reaction started, stopped
- Outcomes attributed to adverse reaction
- Relevant tests/laboratory data (if available)

An identifiable reporter

- Name, initials
- Address
- Contact details
- Qualification (if healthcare professional)

- The expectedness of the reaction is assessed in accordance with the approved product information; the reaction is **defined as expected** if it is included in package insert or the summary of product characteristics (SPC).
- A serious adverse event or reaction is any untoward medical occurrence that at any dose results in:

1- Death

2- Is life-threatening

3- Requires inpatient hospitalization or prolongation of existing hospitalization

4-Persistent or significant disability/incapacity

5- Congenital Anomaly

6- Medically important event or reaction

Causality assessment – WHO scale

- **WHO probability scale**

1- certain

2- Probable / Likely

3- Possible

4- Unlikely

5- Conditional/ Unclassified

6- Unassessable/ Unclassified

NARANJO's Algorithm

Question	Yes	No	Don't know
Are there previous conclusion reports on this reaction?	+1	0	0
Did the adverse reaction appear after the suspect medicine was administered?	+2	-1	0
Did the AR improve when the medicine was discontinued or a specific antagonist was administered?	+1	0	0
Did the AR reappear when medicine was re-administered?	+2	-1	0
Are there alternate causes [other than the medicine] that could solely have caused the reaction?	-1	+2	0

Did the reaction reappear when a placebo was given?	-1	+1	0
Was the medicine detected in the blood [or other fluids] in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar medicines in any previous exposure?	+1	0	0
Was the adverse reaction confirmed by objective evidence?	+1	0	0

NARANJO's Algorithm

Scoring for NARANJO's Algorithm

- > 9 = definite ADR
- 5-8 = probable ADR
- 1-4 = possible ADR
- 0 = doubtful ADR

ADR – How to report-Frequency of reports submission

Reporter	Serious ICSRs	Other ICSRs
Hospitals	**Expedited;** **as soon as possible** **& no later than** **15 calendar days**	▪ Collected & submitted every month by the hospital Pharmacovigilance coordinator using **any** of the above means
Community pharmacies		▪ Collected & submitted every month by the collaborating pharmaceutical distribution company, ▪ May also on individual report basis.
Private clinics		▪ Submitted by the physician on individual report basis, ▪ Also can be delivered to the nearby community pharmacy to be submitted every month by collaborating pharmaceutical distribution company.
Patients		▪ Any report should be submitted as soon as he experienced the reaction, ▪ Or delivered to the nearby community pharmacy to be submitted every month by the collaborating pharmaceutical distribution company
Marketing authorization holders	**Expedited;** **as soon as possible** **& no later than** **15 calendar days** **Using the CIOM form or online**	Included in the PSURs and submitted as follow: ▪ every 6 month for the first 2 years of its international marketing, ▪ then annually for the subsequent 2 years ▪ then every 3 years thereafter

- **In-time reporting**
  - Report the suspected adverse drug reaction as soon as it occurs- the report involves less work and is more accurate.
  - Send the report quickly to the Egyptian Pharmacovigilance center.

What is MedDRA???

Med = medical

D = Dictionary

R = Regulatory

A = activities

MedDRA coding include

All medical terms obtained during product lifecycle

Symptoms

Signs

Disease

Diagnosis

Indications-investigations/procedures

Medical/social history

REFER to LECTURE 2-3 for

Monitoring of scientific & medical literature

When to start and stop searching in the scientific and medical literature

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When to start and stop searching in the scientific and medical literature

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Where to look

Database Searches

Precision and recall

Search construction

Selection of product terms

Limits to a search

Record keeping

Review and selection of articles

Day zero

Duplicates

Questionnaire

▼ Black triangle scheme

- Provides means to identify new medicines
- Encourages the reporting of adverse events associated with their use
- The symbol and text will appear on the PI and CMI, and TGA-related materials

PI: ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events.

CMI: ▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get.

- *Criteria for including a medicinal product in the additional monitoring list:*
- Mandatory scope:
  - Medicinal products that contain a new active substance.
  - Products for which a PASS was requested at the time of marketing authorization
  - Biological medicinal product

- *Criteria for including a medicinal product in the additional monitoring list:*
- Optional scope:
  - Conditions or restrictions with regard to the safe and effective use of the medicinal product
  - Measures for ensuring the safe use of the medicinal product to be included in the risk management system
  - An obligation to conduct a post-authorisation efficacy study

- **Risk management system**

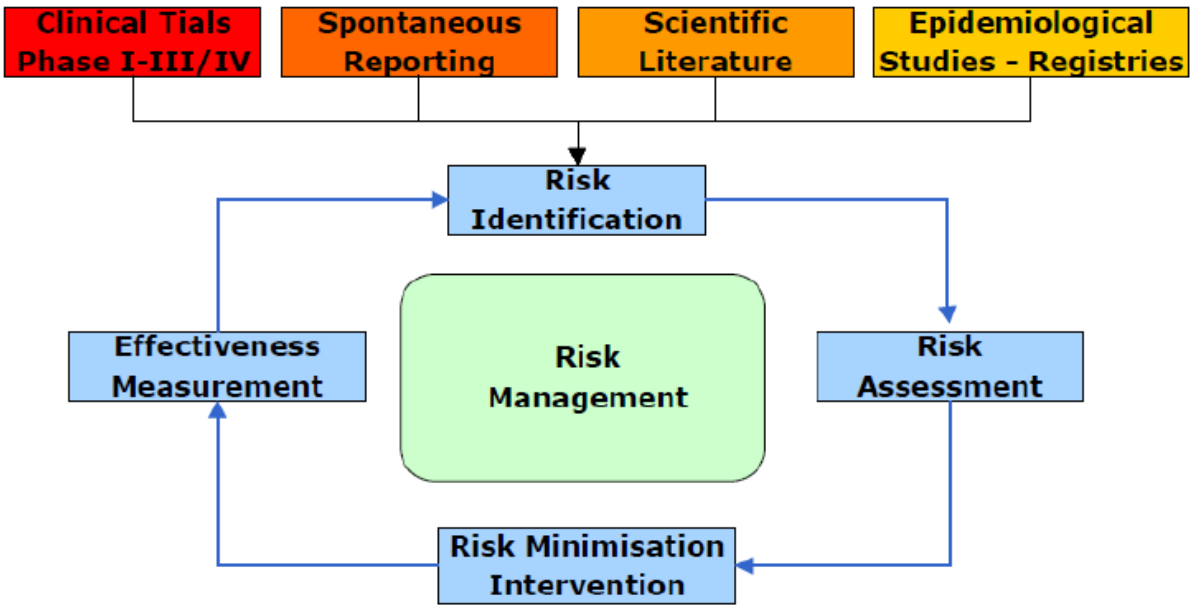
A set of Pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those interventions.

- **Risk minimization activity; synonym: Risk minimization measure**

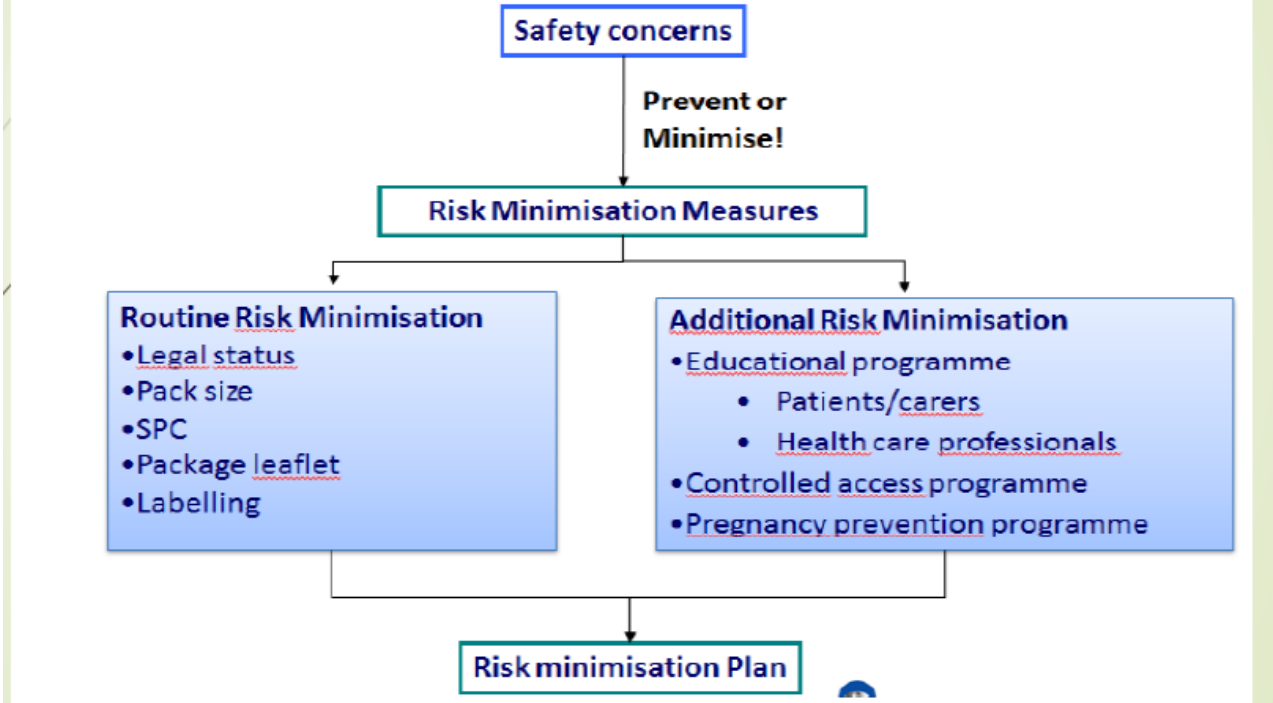
An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine, or to reduce its severity should it occur.

These activities may consist of routine risk minimization (e.g. product information) or additional risk minimization activities (e.g. healthcare professional or patient communications/educational materials).

Risk Management Cycle



Risk Minimisation Measures



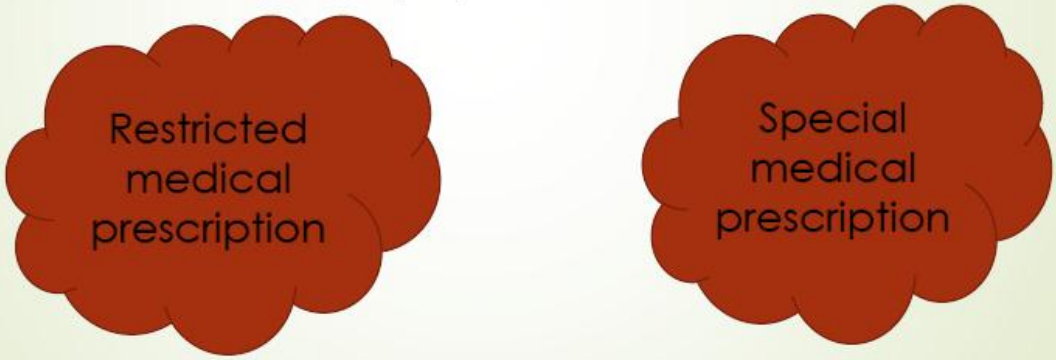
- **The summary of product characteristics (SmPC) and the package leaflet**
- Important tools for risk minimization as they constitute a controlled and standardized format for informing healthcare practitioners and patients about the medicinal product.
- Approved & updated according to the most recent update regarding safety data (as warnings, precautions, undesirable effects, dose or indication modification).

Pack size

- Since every pack size is specifically authorized for a medicinal product, planning the number of –dosage units within each pack, and the range of pack sizes available can be considered a form of routine risk management activity. In theory, controlling the number of –dosage units should mean that patients will need to see a healthcare professional at defined intervals: increasing the opportunity for testing and reducing the length of time a patient is without review.

Legal status

- For medicinal products only available on prescription, additional conditions may be imposed by classifying medicinal products into those available only upon either:



Additional risk minimization measures

- Educational program
  - Educational tools
    - Target healthcare professional
    - Target patients and/or carers
- Controlled access program
- Controlled distribution system
- Pregnancy prevention program
- DHPC

Effectiveness of RMM

- Evaluating the effectiveness of additional risk minimisation measures is necessary to establish whether an intervention has been effective or not, and if not why and which corrective actions are necessary.
- The evaluation should be performed for the additional risk minimisation tools individually and for the risk minimisation programme as a whole.

1- process indicators

Process indicators are necessary to gather evidence that the implementing steps of additional risk minimization measures have been successful.

Process indicators:

1- reaching the target population

2- assessing clinical knowledge

3- assessing clinical actions

2- **outcome indicators**

Outcome indicators provide an overall measure of the level of risk control that has been achieved with any risk minimization measure in place.

- Such an evaluation should involve the comparison of epidemiologic measures of outcome frequency such as incidence rate or cumulative incidence of an adverse reaction.
- Comparisons of frequency before and after the implementation of the risk minimization measures (i.e. pre-post designs) should be considered.

Means of Safety communication

- Documents in lay language

Communication material in lay language (e.g. using a questions & answers format) helps patients and the general public to understand the scientific evidence and regulatory actions relating to a safety concern. Lay language documents should contain the recommendations agreed by the national medicines authority and advice for risk minimization for patients and healthcare professionals in relation to the safety concern, and should be accompanied by relevant background information.

Means of Safety communication

- Press communication

- Press communication includes press releases and press briefings which are primarily intended for journalists.
- National medicines authorities may send press releases directly to journalists in addition to publishing them on their websites. This ensures that journalists, in addition to obtaining information from other sources, receive information that is consistent with the authority‘s scientific assessment. Interaction with the media is an important way to reach out to a wider audience as well as to build trust in the regulatory system.

Means of Safety communication

• Press communication

- Press releases may also be prepared and published by marketing authorization holders. Their press releases may reflect the position of the marketing authorization holder on a safety topic but should also make reference to any regulatory action taken by the national medicines authority. **Relevant ongoing reviews should be mentioned** in any communication by the marketing authorization holder.

Means of Safety communication

• Website

A website is a key tool for members of the public (including patients and healthcare professionals) actively searching the internet for specific information on medicinal products. National medicines authorities as well as marketing authorization holders should ensure that important safety information published on websites under their control is easily accessible and understandable by the public. Information on websites should be kept up-to-date, with any information that is out-of-date marked as such or removed. If possible, the official website of the national medicines authority should contain information on all medicines authorized in its Arab Country.

Means of Safety communication

- Bulletins and newsletters

Bulletins and newsletters provide at regular intervals new information about medicines and their safety and effectiveness. National medicines authorities can reach a large audience with these tools by using web- based and other available means.

Means of Safety communication

- Inter-authority communication

When one medicines authority takes regulatory action on a particular safety concern, other authorities may need to respond to enquiries or communicate on the same issue. The use of inter- authority communication material, such as lines-to-take should be considered. Lines-to-take are documents specifically prepared by a medicines authority to assist its own staff and those of co- operating authorities in responding to external enquires or communicating on a specific safety issue.

Means of Safety communication

• Responding to enquiries from the public

National medicines authorities and marketing authorization holders should have systems in place for responding to enquiries about medicines from individual members of the public. Responses should take into account the information which is in the public domain and should include the relevant recommendations to patients and healthcare professionals issued/agreed by national medicines authorities. **Where questions relate to individual treatment advice, the patient should be advised to contact a healthcare professional**.

Means of Safety communication

Direct healthcare professional communication (DHPC)

A direct healthcare professional communication (DHPC) is defined in this document as a communication intervention by which important safety information is delivered directly to individual healthcare professionals by a marketing authorization holder or a medicines authority (in special cases), to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. DHPCs are not replies to enquiries from healthcare professionals, nor are they meant as educational material for routine risk minimization activities.

Means of Safety communication

Processing of (DHPC)

- When drafting a DHPC, the template and the guidance provided in the annotations in the template should be followed as appropriate.
- The marketing authorization holder should submit the following to the medicines authority (s) in the Arab Country (s) where the products are authorized:
- Draft DHPC
- timetable for disseminating the DHPC: the proposed timetable should be appropriate according to the urgency of the safety concern (usually maximum of 15 calendar days is considered appropriate);
- **dissemination mechanism**: how the DHPC is planned to be disseminated, the proposed mechanism should be selected appropriatly to meet the dissemination timetable.

Means of Safety communication

Processing of (DHPC)

- **the dissemination list** also known as ―intended recipient list‖: the intended recipients HCPs groups may be general practitioners, specialists, pharmacists, nurses; hospitals/ambulatory care/other institutions as appropriate. The list should specify the intended recipients name, specialty and geographical distribution; When defining the target groups of recipients, it should be recognized that it is not only important to communicate with those HCPs who will be able or likely to prescribe or administer the medicinal product, but also to those who may diagnose adverse reactions, e.g. emergency units, poison centres, or to appropriate specialists, e.g. cardiologists. It is also important to consider provision of DHPCs to relevant pharmacists (hospital and /or community) who serve as information providers within healthcare systems and provide assistance and information to Patients, HCPs, including hospital wards and poison centres, as well as the general public.

Means of Safety communication

Processing of (DHPC)

- The MAH should adhere to the Communication Plan agreed with the national medicines authority. Any significant event or problem occurring during the DHPC dissemination which reveals a need to change the Communication Plan or a need for further communication to Healthcare Professionals, this should be notified in a timely manner to national medicines authority to be approved.
- After dissemination of a DHPC, a closing review should be performed by the MAH, a progress report may be submitted upon request of the national medicines authority.

Signal Management

The Report of the Council for International Organizations of Medical Sciences defines a **signal** *as* information that arises from one or multiple sources (including observations and experiments), which suggests a **new** potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to **justify verificatory action.**

SO = only new information related to adverse effects will be considered.

The signal management process can be defined as the **set of activities** performed to determine whether, based on

- an examination of individual case safety reports (ICSRs),
- aggregated data from active surveillance systems or studies,
- literature information or other data sources,
- there are new risks associated with an active substance or a medicinal product or whether known risks have changed.

The signal management process include all steps from initial signal **detection**; through their **validation** and **confirmation**; **analysis** and **prioritization**; and signal **assessment** to recommending action, as well as the **tracking** of the steps taken and of any recommendations made.

The signal management process

Signal Detection

Signal Validation

Signal Analysis and Prioritization

Signal Assessment

Recommendation for action

Exchange of information

Risk management plan

- **Risk Management plan has 3 stages:**
- **Characterization of safety profile including what is known and what is not known.**
- **Planning of pharmacovigilance activities to characterize risk and identify new risk and increase knowledge of safety profile.**
- **Planning and implementation of risk minimization and mitigation and assessment of the effectiveness of these activities**

Integrated & Abridged RMP

Integrated RMP = for innovator

Abridged RMP = for generics

Risk management plan / Abridged RMP

- Data lock point for this RMP :(the last date of collection of data of each section on the document)
- Version number:
- Date of final sign off :(date of termination of all data in all sections of the document)

Post Authorization safety study

- **Post-authorization safety study (PASS)**
- Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.
- A post-authorization safety study may be an interventional clinical trial or may follow an observational, non-interventional study design.
- **Non-interventional trial; synonym: Non-interventional study**
- A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study.

- **Date at which a study commences: date of the start of data collection.**
- **Start of data collection: the date from which information on the first study subject is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts. Simple counts in a database to support the development of the study protocol, for example to inform the sample size and statistical precision of the study, are not part of this definition.**
- **End of data collection: the date from which the analytical dataset is completely available.**

- Analytical dataset: the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.
- Substantial amendment to the study protocol: amendment to the protocol likely to have an impact on the safety, physical or mental well-being of the study participants or that may affect the study results and their interpretation, such as changes to the primary or secondary objectives of the study, to the study population, to the sample size, to the definitions of the main exposure, outcome and confounding variables and to the analytical plan.

- In the research contract, the marketing authorisation holder should address the following aspects
- 1- rationale, main objectives and brief description of the intended methods of the research to be carried out by the investigator(s)
- 2- rights and obligations of the investigator(s) and marketing authorisation holder
- 3- clear assignment of tasks and responsibilities
- 4- procedure for achieving agreement on the study protocol
- 5- publication strategy of interim and final results.

In the research contract, the marketing authorisation holder should address the following aspects

- 6- provisions for meeting the marketing authorisation holder's pharmacovigilance obligations, including the reporting of adverse reactions and other safety data by investigators, where applicable
- 7- storage and availability of analytical dataset and statistical programmes for audit and inspection
- 8- communication strategy for the scheduled progress and final reports
- 9- intellectual property rights arising from the study and access to study data

- Where applicable, legal requirements which are applicable to studies conducted pursuant to an obligation are recommended to studies conducted voluntarily in order to support the same level of transparency, scientific standards and quality standards for all PASS. This applies, for example, to the format of study protocols, abstracts and final study reports and to the communication of study information to national medicines authorities.

Periodic benefit risk evaluation report (PBRER)

Format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorization holder at defined time points during the post-authorization phase.

EU reference date; Union reference date

For medicinal products containing the same active substance or the same combination of active substances, the date of the first marketing authorization in the EU of a medicinal product containing that active substance or that combination of active substances; or if this date cannot be ascertained, the earliest of the known dates of the marketing authorizations for a medicinal product containing that active substance or that combination of active substances.

Development international birth date (DIBD)

Date of first approval (or authorization) for conducting an interventional clinical trial in any country.

- Periodic Safety Update Report with regard to it's definition must be done with regard to the data lock point defined in Union Reference List and submitted on time within 70 calendar day from the DLP if PBRER cover period up to one year and within 90 calendar day from the DLP if PBRER cover period more than one year .

- Data lock point determined by follow up monthly because all data updated monthly on European medicine agency website http://ema.europa.eu/ →Human regulatory→pharmacovigilance→periodic safety update report→List of EURDs and frequency of submission of PBRERs , this list is excel sheet of all active ingredient with all dates concerning data lock point and last submission date for each product

The Development Safety Update Report (DSUR) is intended to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study). This lecture defines the recommended content and format of a DSUR and provides an outline of points to be considered in its preparation and submission.

DSUR

- The DSUR should provide safety information from all ongoing clinical trials and other studies that the sponsor is conducting or has completed during the review period including:
- Clinical trials using an investigational drug.
- Clinical trials conducted using marketed drugs in approved indications (i.e., therapeutic use trials (Phase IV).
- Therapeutic use of an investigational drug.
- Clinical trials conducted to support changes in the manufacturing process of medicinal products.

DSUR

- The DSUR should also include significant other findings pertinent to the safety of the investigational drug, including findings from:
- Observational or epidemiological studies.
- Non-clinical studies (toxicological and *in vitro* studies).
- Related DSURs, if applicable to the investigational drug.
- Manufacturing or microbiological changes.
- Studies recently published in the literature.
- Clinical trials with results indicating lack of efficacy that could have a direct impact on subject safety (e.g., worsening of the underlying condition if the indication is serious or life threatening).
- Any other source of relevant safety findings for products in the same therapeutic class.
- Clinical trials conducted by a co-development partner, if permitted by the contractual agreement.

- *Periodicity and DSUR data lock point*
- The "Development International Birth Date" (DIBD) is used to determine the start of the annual period for the DSUR. This date is the sponsor's first authorization to conduct a clinical trial in any country worldwide. The start of the annual period for the DSUR is the month and date of the DIBD.
- When the sponsor's first clinical trial is conducted in a country without a formal authorization process, the sponsor should designate an appropriate date linked to the commencement of the first clinical trial. Where clinical trials are ongoing in one country and are later initiated in another country, the original DIBD should be maintained and used for all countries in preparing the DSUR.

- *Periodicity and DSUR data lock point*
- The data lock point of the DSUR should be the last day of the one-year reporting period. For administrative convenience, if desired by the sponsor, the data lock point of the DSUR can be designated as the last day of the month prior to the month of the DIBD.

- *Duration of DSUR submissions*
- DSURs should continue to be submitted for as long as indicated by national or regional laws or regulations. When submission of an annual report is no longer required in an individual country or region, the sponsor should indicate that the final DSUR serves as the last annual report for the investigational drug in that country or region. The sponsor should also indicate whether or not clinical trials are continuing elsewhere.

- *Reference safety information*
- *The Investigator's Brochure (IB)* in effect at the start of the reporting period should serve as the reference safety information to determine whether the information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug.
- When an IB is not required by national or regional laws or regulations, the applicable national or regional product label should serve as the reference safety information.

Other topics

STUDY DESIGN

PHARMACOEPIDEMIOLOGY

PV AUDIT

PV INSPECTION

PEDIATRIC VIGILANCE

PV IN RCT

Thanks a lot for your kind cooperation & nice interactions in our PV sessions.
HOPE A LOT OF SUCCESS TO ALL OF YOU
Dr Walaa Arafa